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ZORA URL: <https://doi.org/10.5167/uzh-112270>

Journal Article

Published Version

Originally published at:

Besmens, I S; Fuechsel, F G; Chmiel, C; Meier, C (2015). The Value of SPECT/CT in the Diagnostic Process of Chronic Non-Specific Wrist Pain. *Jacobs Journal of Orthopedics and Rheumatology*, 1(1):4.

Jacobs Journal of Orthopedics and Rheumatology

Research Article

The Value of SPECT/CT in the Diagnostic Process of Chronic Non-Specific Wrist Pain

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Received: 11-30-2014

Accepted: 02-27-2015

Published: 03-26-2015

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Abstract

Purpose: Chronic non-specific wrist pain is a diagnostic challenge. The purpose of this study was to evaluate the benefit of 3D-scintigraphy (Single Photon Emission Tomography (SPECT)) combined with high resolution computed tomography (CT) compared to established standard imaging modalities in a clinical workup. **Methods:** From March 2010 to March 2013, 36 consecutive patients with chronic nonspecific wrist pain undergoing SPECT/CT were reviewed retrospectively. All patients were initially evaluated by non-conclusive standard imaging modalities, such as bi-/multi-planar xrays of the wrist (n=36), CT (n=2), sonography (n=17), MRI (n=10), MR arthrography (n=7), conventional scintigraphy (n=2) or diagnostic arthroscopy (n=2), before SPECT/CT was employed. The new diagnostic information gained by SPECT/CT was grouped according to its effects on the diagnosis and the therapeutic management. These effects were defined as confirmation or correction of the diagnosis and the maintenance or change of treatment. In addition, subjective patient outcome was evaluated with a minimum follow-up of 12 months. **Results:** Twenty-one females, 15 males, mean age 43±12 years, range 20-64 years were included. In 26 the chronic wrist pain originated from an initial trauma, in 10 the onset of symptoms was not trauma related. Twenty had a history of previous wrist surgery. SPECT/CT was performed 6.3 ± 12.9 months after the onset of pain. The findings of SPECT/CT confirmed the previously suspected diagnosis in 4 patients (11%). In 30 patients (83%) the diagnosis was modified. In 2 cases (6%), SPECT/CT was non-conclusive. The information gained by SPECT/CT led to a change of the therapeutic management in 21 patients (58%). Patient satisfaction and ability to work increased after the therapeutic changes based on SPECT/CT findings.

Conclusions: The diagnostic information gained by SPECT/CT in patients with chronic nonspecific wrist pain altered the therapeutic management and patient satisfaction in the majority of our study group.

Level of Evidence: Diagnostic Level IV.

Keywords: Chronic Wrist Pain; SPECT/CT; Imaging

Introduction

Chronic non-specific wrist pain is a diagnostic challenge and its management is often costly and time consuming [1]. Adequate assessment requires certain standardized diagnostic steps, which ideally complement each other while escalating complexity and invasiveness. The Appropriateness Criteria published and last revised in 2012 by the American College of Radiology are evidence-based guidelines to assist physicians and other providers in making the most appropriate imaging or treatment decisions for specific clinical conditions [2]. According to these guidelines 12 different diagnostic measures are recommended for chronic wrist pain with conventional planar x-ray being the most appropriate first-line radiological investigation followed by magnetic resonance imaging (MRI) or computed tomography (CT) with or without contrast. While a Tc-99m bone scan of the wrist is considered “usually not appropriate”, 3D-Scintigraphy (Single Photon Emission Computed Tomography/SPECT) combined with high resolution CT is not even mentioned as a recommended diagnostic tool. However, this new hybrid imaging technique offers a marked diagnostic improvement in many clinical fields [3]. Considering the complex anatomy and multiple articular surfaces of the hand and wrist [4] as well as of the ankle and foot, one can imagine its potential superiority in the diagnostic process compared to other imaging modalities [5]. Therefore, the purpose of this study was to evaluate the potential role of SPECT/CT in the assessment of chronic non-specific wrist pain compared to established imaging modalities.

Methods

Patients

From March 2010 to March 2013, 36 consecutive patients with chronic non-specific wrist pain undergoing SPECT/CT for diagnostic reasons were retrospectively reviewed and included in the study. The analysis was conducted in agreement with the guidelines of the local ethics committee. All patients were managed by a board-certified hand surgeon. The diagnosis of chronic wrist pain was based on the history, clinical examination and radiological studies. Chronic non-specific wrist pain was defined as follows: persisting pain for more than three months with or without previous trauma or surgery without conclusive diagnosis. During the diagnostic process all patients were initially evaluated by non-conclusive standard imaging modalities such as bi-/multi-planar x-rays of the wrist, CT, MRI, MR arthrography, conventional planar scintigraphy or diagnostic arthroscopy. These studies were exclusively motivated by the clinical context at the time and according to the Appropriateness Criteria published by the American College of Radiology [6]. All radiological investigations were evaluated by board-certified radiologists.

Clinical evaluation and follow-up

The analysis of our study group included the history and characteristics of the wrist pain, such as initial trauma, location and duration of symptoms. The diagnostic process, the suspected diagnosis and treatment were analyzed before SPECT/CT was employed. Therefore, the suspected diagnoses were grouped as follows: degenerative changes, inflammation, trauma and non-conclusive findings. The employment of SPECT/CT was considered at the discretion of the responsible hand surgeon. This decision was based on individual judgment only and not according to an established specific diagnostic pathway. The new diagnostic information gained by SPECT/CT was again grouped as described above. The effects of SPECT/CT on the diagnosis and therapeutic management were analyzed. These effects were defined as confirmation or correction of the diagnosis and maintenance or the change of treatment. Treatment changes were grouped as follows: surgery, medical treatment (change of medication, e.g. steroids, dimethyl sulfoxide cream), specific adaptation of ergo/physiotherapy and local infiltration. Simple adaptation of analgesic treatment was not considered as a change of treatment and therefore excluded. The impact of SPECT/CT on the subsequent management and on subjective patient outcome was investigated. As part of an interval follow-up, patients were interviewed at least 12 months after the treatment changes were implemented based on the SPECT/CT findings. These results were compared to the situation before SPECT/CT. A standardized catalogue of questions was used asking patients to grade their satisfaction on a scale of 1-4 (1 (poor), 2 (fair), 3 (good), 4 (excellent)). The degree of pain at follow-up was compared to the situation before SPECT/CT and graded as follows: 1 (more pain), 2 (no change), 3 (moderate pain reduction), 4 (strong pain reduction/no pain at all). The patients' occupation and ability to work at the time before SPECT/CT and after the treatment changes were recorded as well. Furthermore, four illustrative case examples are presented.

Imaging technique and protocols

All patients underwent triphasic bone scintigraphy using a conventional di-phosphonate radiotracer (700 MBq 3,3-Diphosphono-1,2-propanedicarboxylic acid, tetrasodium salt, DPD, TECEOS™CIS Bio Internatl., Gif sur Yvette, France). Arterial and blood-pool phases were acquired in serial planar mode of both hands immediately and 5-10 minutes after injection. Planar scans of the whole body and hands in the late phase (3 hours post-injection) were supplemented by SPECT/CT of the symptomatic hand (SPECT: Low Energy High Resolution/LEHR collimator; 3-head camera: 3°/45 s per step; dual-head camera: 3°/30 s per step, CT scan with high resolution osseous protocol) on commercially available multidetector cameras (IRIX, Philips, Eindhoven, Netherlands; Symbia T16™, Siemens, Erlangen, Germany) with fully diagnostic CT (Somatom

Definition AS 128, Symbia T16, Siemens, Erlangen, Germany). Volume scans (SPECT and CT) were overlaid either off-line or hardware-based on the same dedicated workstation (Syngo 3D, Siemens, Erlangen, Germany). All scans were assessed by the same double-board certified specialist (radiologist/nuclear medicine physician) who was not blinded to the results of the previous imaging studies.

Statistical analysis

Only a descriptive statistical analysis was performed due to the limited number of patients, the lack of a control group and heterogeneous patient characteristics. Data are given as means \pm standard deviation.

Results

Patient characteristics

Mean patient age was 43 ± 12 years (range 20-64 years, 21 women and 15 men). The dominant hand/wrist was affected in 22 patients (61%). In 26 cases (72%), an initial trauma preceded the chronic wrist pain leaving 10 patients (28%) without trauma. However, 14 patients (70%) had previous surgery due to an initial trauma, 6 patients (30%) were operated for reasons other than trauma. The wrist pain was located in 4 designated areas. The local distribution of chronic wrist pain in our patient group is shown in Figure 1. In 73% of our patients the pain was localized around the radial styloid process and/or at the dorsal aspect of the wrist. Twenty-six patients (72%) suffered from load and motion-related pain only, whereas 10 patients (28%) reported to have pain at rest as well.

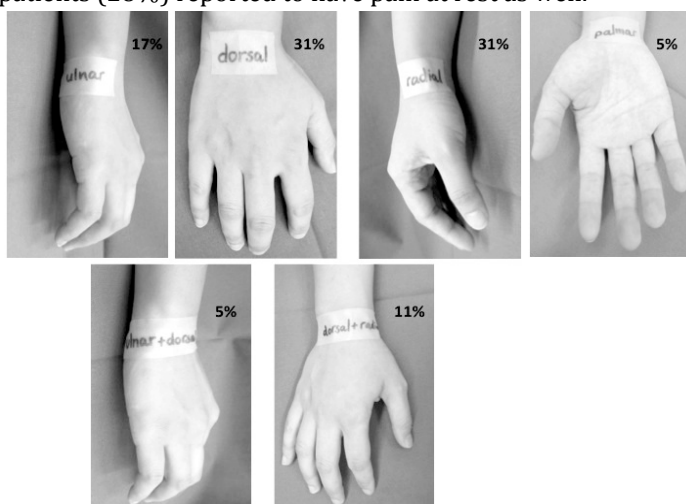


Figure 1. Local distribution of chronic non-specific wrist pain in our patient group.

Imaging previous to SPECT/CT

Overall, mean duration of wrist pain until the SPECT/CT was

performed was 6.3 ± 12.9 months (range 0.1 – 75.4 months). A mean of 1.9 ± 0.9 (range 1-4) non-conclusive radiologic investigations were performed per patient. In total, 36 conventional x-ray series were performed in 31 patients before SPECT/CT was finally employed. We also registered a total of 17 sonographies in 16 patients, 10 MRI in 9 patients, 7 MR arthrographies in 7 patients, 2 CT in 2 patients and 2 scintigraphies in 2 patients after the onset of chronic non-specific wrist pain. The costs ranged from 150 USD for a standard x-ray study of the wrist up to 1020 USD for a MR arthrography. The mean costs for all investigations per patient amounted to 655 ± 605 USD (range 150–2376 USD). In comparison, the costs for a SPECT/CT investigation of the wrist and hand added up to USD 1656 USD in our setting.

Impact of SPECT/CT

The findings on SPECT/CT led to a modification or clarification (i.e. correction) of the diagnosis in 30 patients (83%). In 4 cases (11%) no additional relevant information was obtained (i.e. confirmation), and in 2 cases (6%) the findings of SPECT/CT were nonconclusive. The distribution of diagnostic groups prior and after SPECT/CT is provided in Table 1. Whereas only 17% of the diagnoses was attributed to degenerative changes by standard radiologic imaging, this etiology was predominantly identified by SPECT/CT (64%).

Table 1 Distribution of diagnostic groups prior vs. post SPECT/CT

	Diagnostic groups prior to SPECT/CT (n)	Diagnostic groups post SPECT/CT (n)
Degenerative changes	6 (17%)	23 (64%)
Inflammation	8 (22%)	8 (22%)
Trauma	13 (36%)	3 (8%)
Non-conclusive	9 (25%)	2 (6%)

Detailed information about patient characteristics, the main diagnosis prior and post SPECT/CT and the change of management are provided in Table 2. Either MRI or MR arthrography were performed in 42% of our study group (n=15). After SPECT/CT the clinically relevant diagnosis was specified or corrected in 80% of the cases in this subgroup. Based on the diagnostic information provided by SPECT/CT the course of patient management was changed in 58% of our patients (n=21) (Table 3).

Table 2. Patient characteristics and detailed diagnoses prior and post SPECT/CT with subsequent changes of treatment

#	Age	Sex	Time interval (days, onset of pain – SPECT/CT)	Localization of pain	Previous surgery (x=yes)	Non-conclusive studies (n)	Main diagnosis prior to SPECT/CT	Main diagnosis post SPECT/CT	Change of treatment after SPECT/CT
1	56	♀	80	Radial+palmar	x	1	Unspecific persisting pain over radio-palmar wrist	Radio-lunar degeneration	Change of medication*
2	26	♀	111	Palmar	0	2	Suspected flexor tenosynovitis S/P distal radius fracture Partial SL-lesion	Early stage radio-carpal arthritis	
3	42	♂	286	Dorsal	0	3	Contusion of the carpus with triquetral bone bruise	Contusion of the carpus with triquetral bone bruise	
4	47	♂	66	Radial+palmar	x	1	Radiocarpal arthritis	Stage III SLAC-wrist	Surgery recommended**
5	23	♀	35	Dorsal	0	2	Non-specific wrist pain	Intercarpal and metacarpal arthritis	
6	45	♀	59		x	1	Non-specific diffuse wrist pain S/P carpal tunnel release	Ulna-carpal, radio-carpal, and inter-carpal arthrosis	Ergotherapy
7	22	♀	106	Dorsal	x	5	Wrist pain mainly over tendon compartments 3/4	Radiocarpal arthritis Osteoblastic intraosseous ganglion in the capitate	
8	44	♂	87	Dorsal+ulnar	x	2	S/P SL repair	Loosened bone anchor in the lunate Early stage radioscapoid arthrosis	Surgery
9	31	♂	110	Dorsal	0	3	Load and motion dependent wrist pain	Elevated bone metabolism in the triquetrum, capitate and in the palmar aspect of the radius	
10	56	♀	19	Dorsal+radial	x	1	Non-specific persisting pain over radial wrist S/P release of first dorsal compartment for tenosynovitis S/P distal radius fracture	Activated osteophyte originating from distal radius with contact to the extensor tendons Low active DRUJ arthritis	Surgery
11	50	♀	28	Ulnar+palmar	x	2	Suspected piso-triquetral arthritis S/P diagnostic wrist arthroscopy with partial shaving of the joint capsule	Early stage CRPS	Change of medication*
12	52	♂	159	Ulnar+palmar	x	1	S/P distal radius fracture Suspected piso-triquetral arthritis	Significant radiocarpal arthritis Pisotriquetral arthritis	
13	39	♀	551	Dorsal+radial	x	6	Suspected flexor tenosynovitis S/P filling of intraosseous ganglion of the scaphoid	Delayed healing of an old incomplete fracture of the dorsoradial scaphoid	Change of medication*
14	50	♀	3	Radial+palmar	x	1	Pain over radial styloid S/P release of first compartment twice for de quervain disease	Exostosis of the radial styloid	Local infiltration
15	34	♂	35	Radial+palmar	x	2	S/P scaphoid fracture with Herbert screw fixation	Early stage radiocarpal degeneration	
16	27	♂	2262	Ulnar+palmar	0	2	Non-specific diffus wrist pain	No relevant structural lesion	Ergotherapy
17	48	♀	633	Radial+palmar	0	3	S/P stab injury over MC I S/P several corticoid infiltrations peritendineous MCPJ I	Active inflammatory intracapsular calcification of the MCPJ I	Change of medication*
18	63	♀	163	Radial+palmar	0	1	STT- and basal joint arthritis	Strongly inflammatory active basal joint arthritis and only very low active STT arthritis	Surgery
19	60	♀	244	Ulnar+palmar	x	3	S/P distal radius fracture. S/P wrist arthroscopy and	Intercarpal arthritis	

Table 3 Treatment changes based on SPECT/CT findings (n=21 (58%))

Surgery recommended	7 (19%)
Surgery performed*	5 (14%)
Medical treatment**	9 (25%)
Ergo/Physiotherapy	9 (25%)
Local infiltration	1 (3%)

Table 4 Impact of treatment changes based on SPECT/CT findings

	prior SPECT/CT (number of patients)	post SPECT/CT** (number of patients)
Ability to work*		
100%	9 (35%)	21 (81%)
50%	2 (8%)	3 (11%)
25%	0	1 (4%)
0%	15 (57%)	1 (4%)
Intensity of work***		
Light	7 (27%)	11 (42%)
Medium	8 (31%)	9 (35%)
Heavy****	11 (42%)	6 (23%)



Figure 2. Images of a 63 year old woman with chronic pain over the proximal aspect of the left thumb combined with progressive loss of motion. **A.** Conventional x-rays showed significant degenerative alterations of both the scaphotrapezotrapezoidal (STT) and the saddle joint of the thumb (basal joint arthritis). **B.** Conventional scintigraphy showed tracer uptake in the general area of the distal scaphoid as well as the trapezium and the trapezoid. **C.** Subsequent SPECT/CT demonstrated a severe and metabolically active basal joint arthritis whereas the STT arthritis showed a very subtle tracer uptake only. Based on these findings, a trapezium resection with abductor pollicis longus tendon interposition arthroplasty was performed instead of STT arthrodesis. This resulted in a limited procedure with better restoration of function and excellent pain relief.

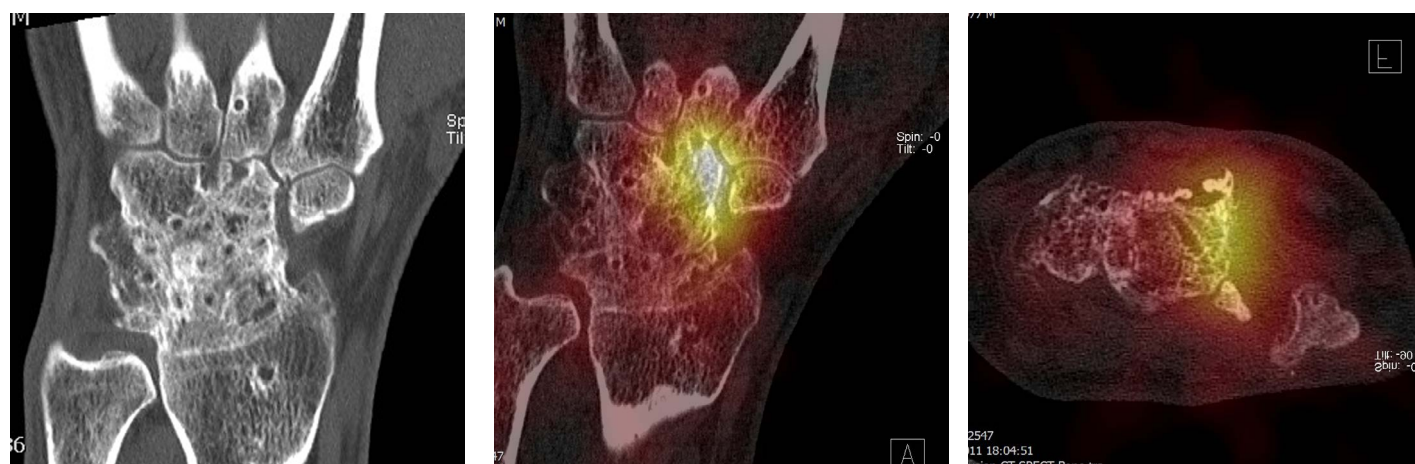


Figure 3. Images of a 36 year old man with a history of multiple surgical procedures of the right hand due to an initial fracture of the scaphoid with subsequent non-union and persistent pain despite resection of the scaphoid and four-corner arthrodesis. **A.** CT demonstrated multiple postoperative and degenerative alterations in this complex anatomical situation. **B** and **C.** SPECT/CT showed a metabolically active osteophyte originating from the capitate that made contact with the extensor tendons and apparently caused an inflammatory reaction of the surrounding soft tissue. Following the diagnostic work-up, the osteophyte was removed in a very limited surgical procedure resulting in a good subjective outcome.

Patient outcome

Twenty-seven patients (75%) were available for follow-up. The mean duration of follow-up was 24 ± 9 months (range 12-46 months). Compared to the time before the SPECT/CT, patient satisfaction improved significantly from 1.9 ± 0.4 (range 1-3) to 3.4 ± 0.7 (range 2-4). Eleven patients (41%) did not report any change of pain at the follow-up, in 9 patients (33%) a moderate pain reduction was observed, and 7 patients (26%)

study group 77% were able to fully work in their previous occupation. The impact on the ability to work and on work intensity is shown in Table 4. At follow-up, the ability to work was improved. Four patients with heavy intensity of manual work (15%) had changed their jobs due to persisting wrist pain and one patient due to a career move unrelated to previous wrist problems. Four illustrative cases are presented in Figure 2-5 to demonstrate the potential benefit of SPECT/CT in complex situations.

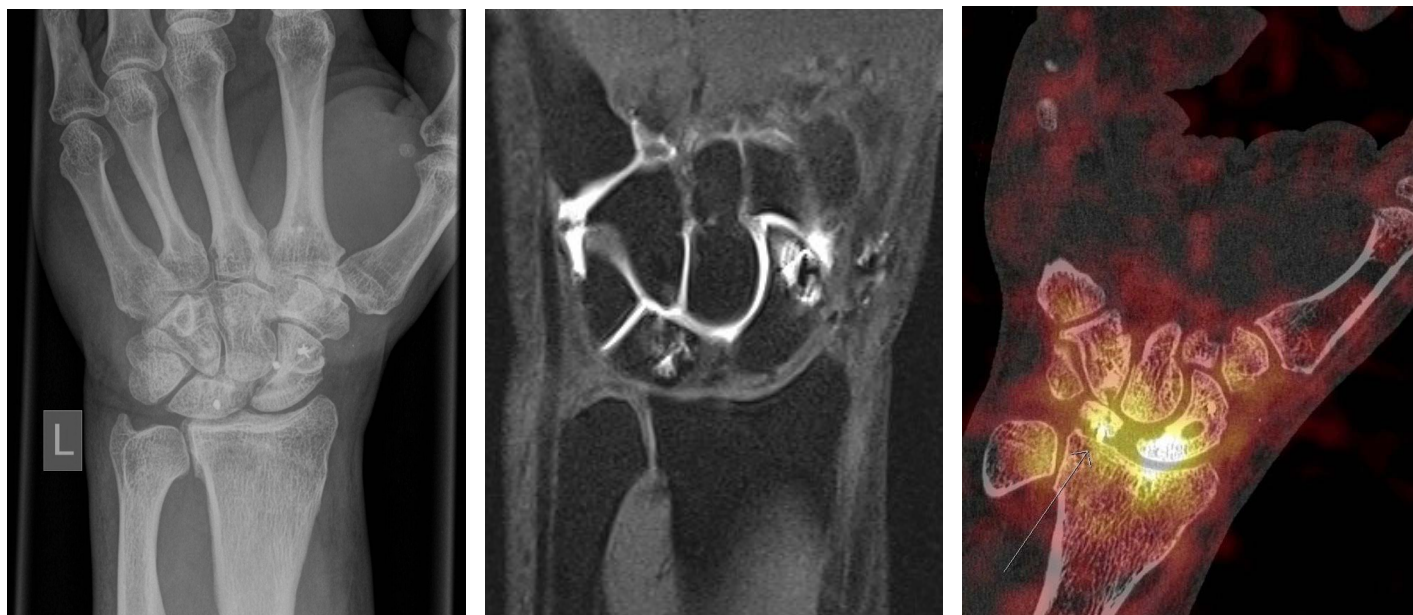


Figure 4. Images of a 45 year old man who complained about persisting pain after having undergone two surgeries to repair a traumatic scapholunar (SL) rupture. The patient presented to our clinic one month after the initial trauma. He received a delayed blatt capsulodesis repair with temporary K-wire fixation. **A.** Postoperative radiographs after K-wire removal showed a persisting SL insufficiency. Thus, a brunelli procedure was performed. Postoperatively, the patient was still complaining about pain over the dorsal aspect of the wrist. **B.** The patient then received an arthro MRI, which showed no pathologies and an intact osseous anatomy. There was no evidence of a persisting SL insufficiency. However, the imaging quality for this imaging technique was impaired in some regions due to the artifacts caused by the implanted metal materials. **C.** SPECT-CT then showed the dislocation of one of the originally implanted mini suture anchors.



Figure 5. Images of a 56 year old woman who suffered from persisting intermittent pain over the first dorsal compartment after surgical release for de quervain disease. **A.** This patient had already sustained a distal radius fracture that had been treated non-operatively one year before. The plain x-rays showed an osseous consolidation of the fracture in an anatomical position. **B.** CT revealed an osteophyte originating from the distal radius but no correlate for this pathology was found intraoperatively. **C.** SPECT- CT then revealed that his osteophyte caused an inflammatory reaction in the surrounding soft tissues. This reaction included the tendons of the abductor pollicis longus and extensor pollicis brevis muscles, thus imitating a persisting de quervain disease.

Discussion

The current study demonstrates that deployment of SPECT/CT in patients with chronic wrist pain and with non-conclusive previous investigations provided new diagnostic information in most patients. Furthermore, this information had a marked impact on further patient management, treatment and subsequently resulted in improved patient satisfaction and ability to work.

Chronic wrist pain

Chronic non-specific pain of the wrist holds a high potential of frustration for both the patient and the attending physician due to the protracted course [7]. Due to the intricate functionality of the hand, minor local lesions can cause major impairments for patients in the execution of their everyday lives [8]. Furthermore, the diagnostic process may be protracted and nonconclusive, resulting in delayed or even absent focused problem-solving treatment.

Diagnostic measures for chronic wrist pain

Modern technologies such as MRI and CT have revolutionized medical imaging. MRI and CT are considered reference-imaging methods for osseous lesions and soft tissue alterations. CT is unmatched with its superb visualization of cortical and trabecular bone [9]. MRI can combine osseous with high contrast soft-tissue differentiation. However, these imaging modalities still provide anatomical information only, while functional or metabolic changes may remain undetected. In contrast, nuclear medicine techniques such as a Tc-99m bone scan provide information about functional or metabolic changes. Unfortunately, these techniques often lack spatial resolution and thus, precise localization of the signal enhancement is frequently not possible, especially in complex regions of the body like the hand. With the introduction of positron emission tomography CT (PET/CT) and SPECT/CT in hybrid cameras, the acquisition of structural and functional information within a single study has been made possible [10]. In complex areas such as the foot or the hand, CT with high resolution protocols improves the diagnostic information due to a better anatomic localization of abnormal tracer uptake on SPECT [11]. The advantages of combined anato-metabolic imaging are striking: The complementary data allows for precise anatomical localization of metabolic alteration [12]. Amongst multiple anatomical pathologies on CT or MRI the metabolically active one can be identified, plausibly being the clinically most relevant [13] one. Also metabolic changes may precede anatomically visible changes [14]. As a result, hybrid imaging modalities are assumed to play an increasingly important role in the diagnosis and staging of human diseases. Since the technology is quite new, no clinical guidelines concerning its use exist currently.

MRI with or without a contrast agent is considered the most appropriate radiologic procedure for most clinical situations in patients with chronic wrist pain after initial normal or non-specific routine radiographs [2]. Other imaging modalities such as CT or ultrasound are only recommended in selected situations. However, the clinically relevant diagnosis in our subgroup with prior MRI or MR arthrography was specified or modified based on the SPECT/CT findings in 80% of the cases with a change of the subsequent management in 47%. With increasing experience with SPECT/CT we also observed an earlier employment of this imaging modality compared to other technologies. Huellner et. al. [15] compared SPECT/CT with MR arthrographies in 21 patients with nonspecific pain of the hand and wrist. Overall, they found a higher sensitivity for MR arthrography (0.86 vs. 0.71) whereas specificity was much better for SPECT/CT (1.00 vs. 0.20). Of interest, sensitivity of SPECT/CT was particularly low for cartilage, ligament pathologies and ganglion cysts. However, such lesions may be over-rated by MRI since some of these lesions are not relevant in a clinical context. Thus, SPECT/CT may be more useful in differentiating clinically relevant lesions from irrelevant findings than as a first-line investigation tool. SPECT/CT may be superior for osseous pathologies as it may detect subtle changes such as bone remodeling, which may be undetected in MRI in early stages. Furthermore, a recent study by Huellner et al suggests that the SPECT/CT is the most specific imaging modality for non-specific wrist pain. Compared to MRI, it yielded a much better specificity in that study. However, sensitivity was better for MRI [16].

Diagnostic infiltration of painful areas with local anesthetic agents may also be used by clinicians during the diagnostic process [17]. It is inexpensive, widely available and if combined with corticosteroids also of therapeutic value. The anesthetic injection may be performed under fluoroscopic guidance to prove the correct location and mixed with contrast to demonstrate its distribution within the articular space. Short-time pain relief following the injection may be a good indicator for a clinically significant intra-articular pathology. In the wrist, there are multiple articulations which are connected with each other, such as in the midcarpal space. By administering anesthetics into this space, the scapholunate and lunotriquetral joints are affected as well [17]. Thus, infiltration of a specific joint may lead to a wider distribution of the anesthetic agent which subsequently reduces its diagnostic value in the evaluation of non-specific chronic wrist pain [18].

Arthroscopy of the radiocarpal and midcarpal joints is still considered the gold standard for the evaluation of intra-carpal pathologies [18]. It allows direct visualization and a therapeutic surgical intervention may be performed during the same procedure. However, it is invasive, expensive and extra-articular pathologies are not addressed.

Our data suggests that SPECT/CT may be successfully employed for non-specific chronic wrist pain. The cost for this investigation modality is considerably higher than for other imaging techniques currently in use. However, its findings have changed or specified the diagnosis, the subsequent clinical management and patient outcome in the majority of our study population.

Costs

The cost for a SPECT/CT is considerably higher than for all other imaging modalities individually. However, SPECT/CT had a high impact on the final relevant clinical diagnosis and the therapeutic regimen in our study group. Chronic wrist pain may cause long-term impairment of the ability to work, especially for craftsmen. An accurate and speedy diagnostic process in combination with effective treatment is crucial. In this context, expensive investigations such as SPECT/CT may lower overall costs for these patients.

However, to our knowledge there is no data available in the literature to support this view. The appropriate indications for the employment of SPECT and its cost-effectiveness in the diagnostic process of chronic non-specific wrist pain require further investigation.

Limitations of the current study

Our observational study was based on retrospective data collection only and the study group was of a rather heterogeneous nature regarding underlying pathology, sequence and timing of different imaging modalities and the final diagnosis. Furthermore, the duration and clinical management of chronic wrist pain varied widely within our study group. The employment of the SPECT/CT was considered at the discretion of the responsible hand surgeon. This decision was based on individual judgement only and not according to an established specific diagnostic pathway. Thus, our data does not allow the assessment of cost effectiveness, the ideal diagnostic sequence and the most appropriate timing for the employment of the SPECT/CT in this patient group. Since we had no control group, we have no outcome data such as patient satisfaction, ability to work or the job situation at follow-up without SPECT/CT and the subsequent therapeutic changes. Thus, we cannot comment on the true impact of SPECT/CT on patient outcome. Variants in hybrid techniques (i.e. online versus offline SPECT/CT) represent the methods available to-date, but may have affected this study due to their different sensitivity and may – at least in part – account for inconclusive studies.

Acknowledgements

The authors declare no conflicts of interest. No benefits in any form have been received or will be received from a commercial

party related directly or indirectly to the subject of this article.

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